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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JAMES W. WILLIAMS, ANITA CHONG, and
W. JAMES WALDMAN

Appeal 2009-000280
Application 09/529,053
Technology Center 1600

Decided:[1] July 15, 2009

Before DEMETRA J. MILLS, ERIC GRIMES, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of treating viral infections. The Examiner has rejected the claims as obvious

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

in view of the prior art or containing new matter. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

This application was the subject of an earlier appeal to this Board (Appeal 2005-0902, decided June 22, 2005). The decision in Appeal 2005-0902 affirmed two rejections based on obviousness, but designated the affirmances as new grounds of rejection. Appellants elected to reopen prosecution and amended the claims. The Examiner rejected the amended claims for obviousness (Office action mailed Dec. 15, 2005) and, after further prosecution, this appeal followed.

Claims 34-42, 45, and 46 are pending and on appeal. Claim 34 and 46 are the only independent claims and read as follows:

> 34. A method of treating a patient suffering from a viral infection comprising administering to said patient a therapeutically effective amount of a leflunomide product and administering to said patient a pyrimidine compound in an amount effective to enhance serum levels of uridine, cytidine or thymidine.
>
> 46. A method of treating a patient suffering from a viral infection comprising administering to said patient (a) a therapeutically effective amount of a leflunomide product and (b) a pyrimidine compound without antiviral activity.

The claims stand rejected as follows:

- Claim 46 under 35 U.S.C. § 112, first paragraph, on the basis that it contains new matter (Answer 3);

• Claims 34, 35, 40, 41, and 45 under 35 U.S.C. § 103(a) as obvious in view of Weithmann,[2] Hammer,[3] and Colacino[4] (Answer 4);

• Claim 39 under 35 U.S.C. § 103(a) as obvious in view of Weithmann, Hammer, Colacino, and Flamand[5] (Answer 5); and

• Claims 34-42 and 45 under 35 U.S.C. § 103(a) as obvious in view of Coghlan,[6] McChesney,[7] Hammer, and Colacino (Answer 6).

NEW MATTER

Issue

The Examiner finds that claim 46 contains new matter because the "limitation 'a pyrimidine compound without antiviral activity' lacks support from the application as originally filed" (Answer 4).

Appellants contend that they have provided declaratory evidence showing that persons of ordinary skill would have recognized a description of pyrimidine compounds without antiviral activity in the Specification as originally filed (Appeal Br. 5-6).

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[2] Weithmann et al., US 5,556,870, issued Sept. 17, 1996.
[3] Scott M. Hammer, *Advances in antiretroviral therapy and viral load monitoring*, 10 AIDS sl-s11 (1996).
[4] Joseph M. Colacino, *Mechanisms for the anti-hepatitis B virus activity and mitochondrial toxicity of fialuridine (FIAU)*, 29 ANTIVIRAL RESEARCH 125-139 (1996).
[5] Flamand et al., *Human Herpesvirus 6 Induces Interleukin-1β and Tumor Necrosis Factor Alpha, but Not Interleukin-6, in Peripheral Blood Mononuclear Cell Cultures*, 65 J. VIROLOGY 5105-5110 (1991).
[6] Coghlan et al., WO 94/24095, published Oct. 27, 1994.
[7] McChesney et al., *An Evaluation Of Leflunomide In The Canine Renal Transplantation Model*, 57 TRANSPLANTATION 1717-1711 (1994).

The issue with respect to this rejection is: Did the Examiner err in finding that the Specification does not provide an adequate description of a pyrimidine compound without antiviral activity?

Findings of Fact

1. The Specification states that leflunomide can be "co-administered with a pyrimidine, such as uridine, in order to reduce its potential toxicity while maintaining its therapeutic effectiveness" (Spec. 20: 2-3).

2. The Specification states that,"[a]s used herein, a 'pyrimidine' includes compounds useful either directly or as intermediates in pathways for supplying pyrimidine nucleotides (uridine, cytidine and thymidine)" (*id.* at 20: 12-14).

3. The Specification states that a "preferred pyrimidine is uridine. Other suitable pyrimidines include the pyrimidine intermediates orotic acid and orotidine." (*Id.* at 20: 14-16.)

4. Appellants filed a declaration under 37 C.F.R. § 1.132 by Walter Atwood, PhD (Atwood declaration, filed Dec. 21, 2006).

5. Dr. Atwood declared that "[o]ne of ordinary skill in the art as of March 11, 1998 would have understood, from reading the language quoted in [FF 1], that the inventor(s) contemplated administration of a pyrimidine compound *to reduce the toxicity of the leflunomide product, not for any anti-viral effect*" (Atwood declaration, ¶ 7).

6. Dr. Atwood declared that the "definition of pyrimidine compound [in FF 2] confirms that the contemplated pyrimidine compounds *would not have anti-viral activity*. . . . Uridine, cytidine and thymidine are naturally

occurring nucleosides, which are used as a 'building block' for DNA or RNA, and which have no anti-viral effect." (*Id.* at ¶ 8.)

7. Dr. Atwood concludes that "one of ordinary skill in the art as of March 11, 1998, upon reading the application, would have understood that the inventors were claiming the administration of pyrimidine compounds *without antiviral activity*" (*id.* at ¶ 11).

Principles of Law

The examiner "'bears the initial burden . . . of presenting a prima facie case of unpatentability.' Insofar as the written description requirement is concerned, that burden is discharged by 'presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.'" *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996) (citation omitted).

"If . . . the specification contains a description of the claimed invention, albeit not *in ipsis verbis* (in the identical words), then the examiner . . ., in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient." *Id.*

Analysis

The Specification defines "pyrimidines" as compounds that are useful for supplying pyrimidine nucleotides (uridine, cytidine, and thymidine). The Specification also describes administration of a pyrimidine along with leflunomide in order to reduce the toxicity of leflunomide, not as an antiviral agent. Dr. Atwood has declared that persons of ordinary skill in the art

would have understood the Specification to describe pyrimidine compounds that were not intended or expected to have antiviral activity.

Based on the evidence of record, we conclude that the Examiner has not adequately explained why one of ordinary skill in the art would not consider the Specification's description sufficient to describe pyrimidine compounds without antiviral activity.

Conclusion of Law

The Examiner erred in finding that the Specification does not provide an adequate description of a pyrimidine compound without antiviral activity.

OBVIOUSNESS

Issue

The Examiner has rejected claims 34-42 and 45 under 35 U.S.C. § 103(a): claims 34, 35, 40, 41, and 45 as obvious in view of Weithmann, Hammer, and Colacino (Answer 4); claim 39 as obvious in view of Weithmann, Hammer, Colacino, and Flamand (Answer 5); and claims 34-42 and 45 as obvious in view of Coghlan, McChesney, Hammer, and Colacino (Answer 6).

The Examiner finds that Weithmann, Coghlan, and McChesney teach treating viral infections by administering leflunomide to a patient (Answer 4, 6-7). The Examiner finds that Hammer and Colacino teach pyrimidine compounds that are antiviral agents (*id.* at 4-5, 7). The Examiner concludes that it would have been obvious to administer leflunomide in combination with the antiviral agents taught by Hammer and Colacino because Hammer teaches the benefits of combination therapy (*id.* at 5, 7).

Appellants contend that the antiviral activity of the nucleoside analogs taught by Hammer and Colacino shows that they do not "enhance serum levels of uridine, cytidine or thymidine," as required by the claims, and the Examiner has provided no evidence that they have the recited effect (Appeal Br. 9-11).

The dispositive issue for all of these rejections is: Does the evidence of record support the Examiner's finding that the pyrimidine analogs taught by Hammer and Colacino would "enhance serum levels of uridine, cytidine or thymidine," as recited in claim 34?

Additional Findings of Fact

8. Hammer discloses nucleoside analog reverse transcriptase inhibitors useful in antiretroviral therapy (Hammer S2, right col.).

9. Four of the specific nucleoside analog reverse transcriptase inhibitors discussed by Hammer – zidovudine, zalcitabine, stavudine, and lamivudine – are pyrimidine analogs (*id.* at S3, Fig. 2).

10. Colacino discloses that "[f]ialuridine (FIAU) is a thymidine nucleoside analog with activity against various herpesviruses and hepatitis B virus (HBV) in vitro and in vivo" (Colacino 125, abstract).

11. Colacino discloses that FIAU can be metabolized to its phosphorylated derivatives FIAU-MP, FIAU-DP, and FIAU-TP (*id.* at 126, Fig. 2).

12. Colacino discloses that FIAU-MP can be metabolized to FAU-MP (*id.*).

13. FAU is structurally identical to FIAU except for the replacement of an iodine atom (I) in FIAU with a hydrogen atom (H) in FAU (*id.* at 125, Fig. 1).

14. Colacino discloses that FAU-MP can be metabolized to FMAU-MP (*id.* at 126, Fig. 2).

15. FMAU is structurally identical to FAU except for the replacement of a hydrogen atom (H) in FAU with a methyl group (CH_3) in FMAU (*id.* at 125, Fig. 1).

16. None of the metabolic pathways disclosed by Colacino include uridine, cytidine, or thymidine.

17. Appellants cite Walker[8] as evidence that nucleoside analogs would not be expected to increase the supply of naturally occurring nucleotides (Appeal Br. 10).

18. Walker discloses that "[l]ong-term side effects of antiretroviral therapy are attributed to the mitochondrial (mt) toxicity of nucleoside analogue reverse transcriptase inhibitors (NRTIs) and their ability of deplete mtDNA" (Walker M117, abstract).

19. Walker discloses that NRTIs include zidovudine (*id.* at M1117, right col.).

20. Walker discloses that NRTIs compete with natural nucleoside trisphosphates for binding to polymerase γ and cause chain termination of mtDNA (*id.* at M117, paragraph bridging the columns).

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[8] Ulrich A. Walker and Nils Venhoff, *Uridine in the prevention and treatment of NRTI-related mitochondrial toxicity*, 10 ANTIVIRAL THERAPY M117-M123 (2005).

21. Walker discloses that "[a]s mtDNA encodes for subunits of the mt respiratory chain, mtDNA depletion therefore results in respiratory chain dysfunction" (*id.* at M118, left col.).

22. Walker discloses that a defect in the respiratory chain results in pyrimidine depletion because it disrupts the activity of the enzyme dihydroorotate-dehydrogenase, which is necessary for the *de novo* synthesis of all cellular pyrimidines (*id.* at M118, paragraph bridging the columns).

23. Walker discloses that uridine can "prevent the onset of a severe mtDNA depletion and thereby normalize the synthesis of mtDNA-encoded respiratory chain subunits" (*id.* at M119, left col.).

Principles of Law

A proper § 103 analysis requires "a searching comparison of the claimed invention – including all its limitations – with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995).

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993).

> [W]here the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.

In re Best, 562 F.2d 1252, 1254-55 (CCPA 1977).

However, "the examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic of the prior art" before the burden is shifted to the applicant to disprove the inherency. *Ex parte Skinner*, 2 USPQ2d 1788, 1789 (BPAI 1986).

Analysis

The Examiner's position is that "[a]ll of the pyrimidine compounds on the record have a pyrimidine moiety, and would have been reasonably expected to add an intermediate in pathways for supplying pyrimidine nucleotide[s]" (Answer 10). The Examiner, however, has cited no evidence to support the reasonableness of this expectation.

Appellants assert that the nucleoside analogs disclosed by Hammer and Colacino do not enhance serum levels of uridine, cytidine, or thymidine (Appeal Br. 9). Appellants reason that nucleoside analogs "exert their anti-viral effect precisely because they are non-natural analogs. In other words, the basis for their anti-viral activity is their ability to act *unlike* natural nucleosides." (*Id.*) Appellants cite Walker, among others, as evidence that administering nucleoside analogs would not be expected to reduce leflunomide toxicity by increasing the supply of naturally occurring nucleosides (*id.* at 10).

We conclude that the Examiner's position is not supported by a preponderance of the evidence of record. The Examiner has provided no evidence to show that pyrimidine analogs are metabolized to naturally occurring pyrimidines *in vivo*. Appellants' position is supported by at least Colacino and Walker.

Colacino discusses metabolism of the pyrimidine analog FIAU but does not disclose any metabolic step that converts FIAU into a naturally occurring pyrimidine. Walker indicates that nucleoside analog reverse transcriptase inhibitors (NRTIs), including zidovudine (a pyrimidine analog), block de novo synthesis of pyrimidines by competing with naturally occurring pyrimidines. Walker discloses that exogenous uridine can counteract the toxic effects of NRTIs.

Neither Colacino nor Walker disclose that pyrimidine analogs are converted into naturally occurring pyrimidines, and the toxic effects discussed by Colacino and Walker are evidence that they are not, since conversion to naturally occurring pyrimidines would eliminate the toxic effects of the pyrimidine analogs in cells. In addition, Walker's disclosure that the toxic effect of NRTIs, including pyrimidine analogs, can be mitigated by uridine, is evidence that the pyrimidine analogs are not converted into naturally occurring pyrimidines, because such conversion would bypass the catalytic step blocked by the pyrimidine analogs and avoid the toxic effect. Walker's disclosure that pyrimidine analogs are toxic, and that uridine (a naturally occurring pyrimidine) counteracts that effect, is evidence that pyrimidine analogs are not converted to naturally occurring pyrimidines.

The Examiner has also rejected claim 39, which depends on claim 34, as obvious in view of Weithmann, Hammer, Colacino, and Flamand (Answer 5); and claims 34-42 and 45 as obvious in view of Coghlan, McChesney, Hammer, and Colacino (Answer 6). Both rejections depend on Hammer and Colacino for the disclosure of pyrimidines that enhance serum

levels of uridine, cytidine or thymidine, and therefore suffer the same deficiency as the rejection based on Weithmann, Hammer, and Colacino.

Conclusion of Law

The evidence of record does not support the Examiner's finding that the pyrimidine analogs taught by Hammer and Colacino would "enhance serum levels of uridine, cytidine or thymidine," as recited in claim 34.

SUMMARY

We reverse the rejection the rejection of claim 46 under 35 U.S.C. § 112, first paragraph, and the rejections of claims 34-42 and 45 under 35 U.S.C. § 103(a).

REVERSED

cdc

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